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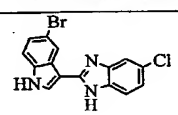
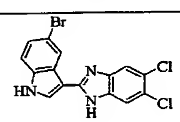
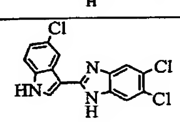
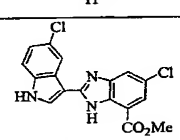
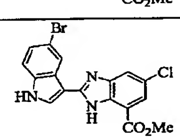
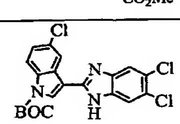
*[Continued on next page]*

(54) Title: INDOLYL-BENZIMIDAZOLE ANTIBACTERIALS, AND METHODS OF USE THEREOF

MIC Values Against MRSA for Certain Aryl-Benzimidazoles of the Present Invention

| Aryl-Benzimidazole | MIC Value Against MRSA (μg/mL) |
|---|---|
|  | <10 |
|  | <1 |
|  | <1 |
|  | >25 |
|  | >25 |
|  | <10 |

**(57) Abstract:** The present invention relates to heteroaromatic compounds, preparations thereof, and their use as antibacterials or antiinfectives or both. One aspect of the present invention relates to novel aryl-benzimidazole compounds. A second aspect of the present invention relates to the use of aryl-benzimidazole compounds or formulations thereof, as antibacterials or antiinfectives or both.

WO 00/78761 A1

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# *Indolyl-Benzimidazole Antibacterials, and Methods of Use Thereof*

## *Related Applications*

This application claims the benefit of priority to United States Provisional Patent Application serial number 60/140,570, filed June 23, 1999.

## *Background of the Invention*

A number of structural classes of compounds with antibacterial properties are known. Historically, the most important classes of antibacterials have been the β-lactams, macrolides, lincosamides, aminoglycosides, tetracyclines, polypeptides, and sulfonamides. The bulk of these antibacterial compounds were isolated originally from molds, fungi or bacteria; synthetic and semi-synthetic compounds, additionally, have proven to be efficacious in the treatment of bacterial infections. In the broadest possible sense, known antibacterials work by influencing at least one of the following processes or characteristics of the bacterial cell: cell wall synthesis; protein synthesis; nucleic acid synthesis; cellular metabolism; and cytoplasmic membrane permeability. Brief descriptions follow of the mechanisms of action of members of each of the aforementioned classes of antibacterials.

The β-lactam antibiotics inhibit penicillin binding proteins (PBPs). The PBPs are ubiquitous bacterial enzymes that are involved in cell wall biosynthesis (reviewed in Waxman et al., 1983 Annual Review of Biochemistry 58:825-869; Georgopapadkou et al., 1983 Handbook of Experimental Pharmacology 67:1-77; and Ghuysen, 1991 Annual Review of Microbiology 45:37-67); inhibition of these proteins disrupts the biosynthesis of the bacterial cell wall. Specifically, these compounds act as substrate analogs for the PBPs and form an acyl enzyme intermediate. This acyl enzyme intermediate is resistant to subsequent hydrolysis and ties up the enzyme in a relatively long-lived inactive form. Bacteria have responded to the widespread use of β-lactam antibiotics by evolving a class of β-lactam hydrolyzing enzymes known as β-lactamases. These enzymes are one of the sources of drug resistance now being observed in a number of bacterial diseases including tuberculosis, malaria, pneumonia, meningitis, dysentery, bacteremia, and various venereal diseases.

The macrolides are a family of antibiotics whose structures contain large lactone rings linked through glycoside bonds with amino sugars. The most important members of the group are erythromycin and oleandomycin. Erythromycin is active against most Gram-positive bacteria, *Neisseria*, *Legionella* and *Haemophilus*, but not against the *Enterobacteriaceae*. Macrolides inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit. Binding inhibits elongation of the protein by peptidyl transferase or prevents translocation of the ribosome or both. Macrolides are bacteriostatic for most

bacteria but are bactericidal for a few Gram-positive bacteria.

The lincosamides are sulfur-containing antibiotics isolated from *Streptomyces lincolnensis*. There are two important lincosamides: lincomycin and clindamycin. Clindamycin is preferred over lincomycin due to its greater potency, fewer adverse side effects, and its more favorable pharmacokinetic properties. Bacterial resistance and cross resistance to clindamycin have begun to emerge. The lincosamides are active against Gram-positive bacteria particularly *cocci*, but also non-spore forming anaerobic bacteria, *Actinomycetes*, *Mycoplasm* and some *Plasmodium*. The lincosamides bind to the 50S ribosomal subunit and thereby inhibit protein synthesis. These drugs may be bacteriostatic or bactericidal depending upon several factors, including their local concentration.

Aminoglycosides are important antibacterials used primarily to treat infections caused by susceptible aerobic Gram-negative bacteria. Unfortunately, they have a narrow margin of safety, producing characteristic lesions in kidney, cochlea, and vestibular apparatus within the therapeutic dose range. Because they are polycations, the aminoglycosides cross cellular membranes very poorly.

The tetracyclines consist of eight related antibiotics which are all natural products of *Streptomyces*, although some can now be produced semi-synthetically. Tetracycline, chlortetracycline and doxycycline are the best known members of this class. The tetracyclines are broad-spectrum antibiotics with a wide range of activity against both Gram-positive and Gram-negative bacteria. The tetracyclines act by blocking the binding of aminoacyl tRNA to the A site on the ribosome. Tetracyclines inhibit protein synthesis on isolated 70S or 80S (eukaryotic) ribosomes, and in both cases, their effect is on the small ribosomal subunit. Most bacteria possess an active transport system for tetracycline that will allow intracellular accumulation of the antibiotic at concentrations 50 times as great as that in the surrounding medium. This system greatly enhances the antibacterial effectiveness of tetracycline and accounts for its specificity of action, since an effective concentration is not accumulated in host cells. Thus a blood level of tetracycline which is harmless to mammalian tissues can halt protein synthesis in invading bacteria. The tetracyclines have a remarkably low toxicity and minimal side effects in mammals. The combination of their broad spectrum and low toxicity has led to their overuse and misuse by the medical community and the wide-spread development of resistance has reduced their effectiveness. Nonetheless, tetracyclines still have some important uses, such as in the treatment of Lyme disease.

The polypeptide antibacterials have in common their basic structural elements -- amino acids. Representatives of this class include vancomycin, and bacitracin. Vancomycin can be used to treat both systemic and gastrointestinal infections, whereas because of serious systemic toxicities, bacitracin is limited to topical applications. Vancomycin inhibits

bacterial cell wall synthesis by inhibiting peptidoglycan synthase, apparently by binding to D-alanyl-D-alanine, a component of the cross-link between chains. This action inhibits peptidoglycan chain elongation, and as might be expected, the effect is bactericidal for most organisms if they are dividing rapidly. Because it does not target penicillin-binding enzymes, vancomycin is not cross-resistant with the β-lactams. Bacitracin is a narrow spectrum antibiotic which inhibits cell wall biosynthesis by inhibiting lipid pyrophosphatase; this enzyme is involved in transmembrane transport of peptidoglycan precursors.

The sulphonamides are usually bacteriostatic and arrest cell growth by inhibiting bacterial folic acid synthesis. They are effective against sensitive strains of Gram-negative and Gram-positive bacteria, *Actinomyces*, *Nocardia* and *Plasmodia*. However, extensive clinical use of sulfonamides over many years has resulted in a high level of resistance and their current use is limited.

Antibacterial resistance is a global clinical and public health problem that has emerged with alarming rapidity in recent years and undoubtedly will increase in the near future. Resistance is a problem in the community as well as in health care settings, where transmission of bacteria is greatly amplified. Because multiple drug resistance is a growing problem, physicians are now confronted with infections for which there is no effective therapy. The morbidity, mortality, and financial costs of such infections pose an increasing burden for health care systems worldwide, but particularly in countries with limited resources. Strategies to address these issues emphasize enhanced surveillance of drug resistance, increased monitoring and improved usage of antimicrobial drugs, professional and public education, development of new drugs, and assessment of alternative therapeutic modalities.

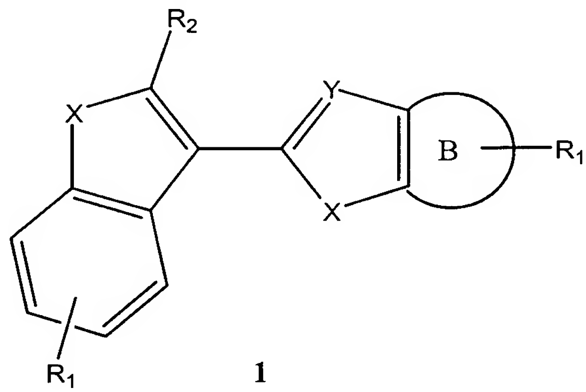
### *Summary of the Invention*

A need exists for alternative and improved agents for the treatment of bacterial infections, particularly for the treatment of infections caused by resistant strains of bacteria, e.g., penicillin-resistant, methicillin-resistant, ciprofloxacin-resistant, and/or vancomycin-resistant strains, as well as for the decontamination of objects bearing such organisms, e.g., non-living matter, hospital equipment, walls of operating rooms, and the like.

Generally, the present invention provides compositions of matter, methods and pharmaceutical preparations for inhibiting the growth of bacterial microorganisms and infections thereof, such as Gram-positive bacteria, including *Staphylococcus*, *Streptococcus*, and *Enterococcus*, and Gram-negative bacteria, including *Enterobacteriaceae*, *Mycobacterium*, *Neisseria*, *Pseudomonas*, *Shigella*, *Escherichia*, *Bacillus*, *Micrococcus*, *Arthrobacter*, and *Peptostreptococcus*. For instance, certain compounds of the present invention are useful in the treatment of infections caused by methicillin-resistant strains of bacteria, e.g. methicillin-resistant strains of *Staphylococcus aureus* (MRSA; *Micrococcus*

*pyogenes var. aureus*), ciprofloxacin-resistant strains of bacteria, e.g. ciprofloxacin-resistant strains of *Staphylococcus aureus* (CRSA), and vancomycin-resistant strains of bacteria, e.g. vancomycin-intermediate-resistant *Staphylococcus aureus* (VISA) and vancomycin-resistant *Enterococcus faecalis* (VREF). In preferred embodiments, the present invention can be used to inhibit bacterial infections caused by Gram-positive bacteria, for example, *S. aureus*, *S. epidermidis*, *S. pneumonia*.

In certain embodiments, the compounds of the present invention are represented by general structure **1**, or a pharmaceutically acceptable salt and/or prodrug thereof:




**1**

wherein

X represents independently for each occurrence NR, O or S;

Y represents N or NO;

B represents a fused ring selected from the group consisting of monocyclic or polycyclic cycloalkyls, cycloalkenyls, aryls, heteroaryls, and heterocyclic rings, said rings comprising from 4 to 8 atoms in a ring structure;

R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, hydroxyl, alkoxyl, -$(CH_2)_n$Oalkyl, -$(CH_2)_n$Oaryl, formyl, acyl, -C(O)Oalkyl, -OC(O)Oaryl, -C(O)NHalkyl, -OC(O)NHaryl, alkylsulfonyl, -$(CH_2)_n$C(O)N$(R_{80})_2$, -$(CH_2)_n$-CH(OH)-CH$_2$N$(R_{80})_2$, or -$(CH_2)_n$-$R_{80}$;

B may be unsubstituted or substituted with $R_1$ any number of times up to the maximum number permitted by the structure of B;

the B-ring of the 1-X-bicyclo[4.3.0]nonatetradien-3-yl moiety may be unsubstituted or substituted with up to four instances of $R_1$;

$R_1$, when present, is selected independently for each occurrence from the set consisting of Me, lower alkyl, alkenyl, -C≡C-$R_{80}$, lower heteroalkyl, aryl, heteroaryl, aralkyl,

heteroaralkyl, cycloalkyl, heterocycloalkyl, halogen, hydroxyl, alkoxyl, nitro, nitroso, cyano, acyl, acylamino, amido, alkoxycarbonyl, sulfonyl, sulfonamido, acyloxy, $-(CH_2)_nC(O)N(R_{80})_2$, $-(CH_2)_n-CH(OH)-CH_2N(R_{80})_2$, and $-(CH_2)_n-R_{80}$;

$R_2$ represents H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, hydroxyl, alkoxyl, $-(CH_2)_n$Oalkyl, $-(CH_2)_n$Oaryl, formyl, acyl, -C(O)Oalkyl, -OC(O)Oaryl, -C(O)NHalkyl, -OC(O)NHaryl, sulfonyl, $-(CH_2)_nC(O)N(R_{80})_2$, $-(CH_2)_n-CH(OH)-CH_2N(R_{80})_2$, or $-(CH_2)_n-R_{80}$;

$R_{80}$ represents independently for each occurrence H or an optionally substituted alkyl, acyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl moiety; and

n independently for each occurrence is an integer in the range 0 to 8 inclusive.

In certain embodiments, compounds represented by generalized structure **1** display minimum inhibitory concentrations (MICs) below 25 μg/mL against certain Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus*, ciprofloxacin-resistant *Staphylococcus aureus*, and/or *Streptococcus pneumoniae*. In more preferred embodiments, the compounds have MIC values less than 10 μg/mL or even less than 1 μg/mL against such bacteria, particularly against methicillin-resistant *Staphylococcus aureus* or ciprofloxacin-resistant *Staphylococcus aureus* or both.

In certain embodiments, compounds represented by generalized structure **1** display minimum inhibitory concentrations (MICs) below 25 μg/mL against certain Gram-negative bacteria. In more preferred embodiments, the compounds have MIC values less than 10 μg/mL or even less than 1 μg/mL against such bacteria.

One aspect of the present invention relates to novel aryl-benzimidazole compounds. A second aspect of the present invention relates to the use of aryl-benzimidazole compounds as antibacterials or antiinfectives or both. Specifically, the invention, as described herein, is directed to the use of small (e.g., $M_r < 1$ kD) organic molecules, i.e., 2-aryl-benzimidazoles and substituted derivatives thereof, and pharmaceutical formulations thereof, as antibacterials. Specifically proposed as antibacterial agents are compounds based on 2-(3-indolyl)-benzimidazole and derivatives thereof. As described herein, a number of the antibacterials have *in vitro* minimum inhibitory concentrations (MICs) at or below single-digit micromolar concentrations in assays against cultures of methicillin-resistant *Staphylococcus aureus* (MRSA).

### *Brief Description of the Figures*

**Figure 1** depicts certain aryl-benzimidazoles of the present invention that were synthesized using a procedure outlined in Example 1.

**Figure 2** depicts certain aryl-benzimidazoles of the present invention that were synthesized using a procedure outlined in Example 1.

**Figure 3** depicts certain aryl-benzimidazoles of the present invention that were synthesized using a procedure outlined in Example 1.

**Figure 4** depicts certain aryl-benzimidazoles of the present invention prepared by hydrazinolysis of certain aryl-benzimidazoles depicted in Figures 1 and 2.

**Figure 5** depicts certain aryl-benzimidazoles of the present invention prepared from an aryl-benzimidazole depicted in Figure 2 by saponification followed by amide formation.

**Figure 6** depicts certain aryl-benzimidazoles of the present invention prepared from an aryl-benzimidazole depicted in Figure 3 by saponification followed by amide formation.

**Figure 7** depicts certain aryl-benzimidazoles of the present invention and their MIC values against MRSA.

**Figure 8** depicts certain aryl-benzimidazoles of the present invention and their MIC values against MRSA.

**Figure 9** depicts certain aryl-benzimidazoles of the present invention and their MIC values against MRSA.

**Figure 10** depicts certain aryl-benzimidazoles of the present invention and their MIC values against MRSA.

## *Detailed Description of the Invention*

In the last decade, the frequency and spectrum of antimicrobial-resistant infections has increased. Certain infections that are essentially untreatable are reaching epidemic proportions in both the developing world and institutional settings in the developed world. Antimicrobial resistance is manifested in increased morbidity, mortality, and health-care costs. *Staphylococcus aureus* is an significant cause of nosocomial infection, particularly nosocomial pneumonia, surgical wound infection, and bloodstream infection (Panlilio et al., Infect. Cont. Hosp. Epidemiol. 13: 582-586 (1992)). Other pathogens commonly associated with nosocomial infection include, but are not limited to, *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus* spp., *Enterobacter* spp., coagulase-negative *staphylococci* (CNS). As described above, a considerable amount of effort has been devoted to developing bacteriostatic and bactericidal agents with activity against these and other microorganisms.

The present invention relates to heterocyclic antibacterial agents with antimicrobial activity and preparations thereof, including antibacterial activity against both sensitive and resistant strains. The subject antibacterial compounds comprise two distinct heterocycles that are covalently linked to each other, preferably via a carbon-carbon single bond. Generally, the compounds of the present invention are aryl-benzimidazoles. In certain embodiments, the

individual heterocyclic moieties are benzimidazole and indole nuclei interconnected at their respective 2- and 3-positions. The remaining positions of the 2-benzimidazolyl and aryl nuclei of the subject compounds may independently be unsubstituted or substituted with a variety of groups.

Compounds of the present invention are effective against a number of human and veterinary pathogens, including Gram-positive bacteria such as multiply-resistant staphylococci, streptococci and enterococci, and are expected to be active against Gram-negative organisms as well, such as *Bacteroides spp.* and *Clostridia spp.* species, and acid-fast organisms such as *Mycobacterium tuberculosis*, *Mycobacterium avium* and other *Mycobacterium spp.*, and in organisms such as *Mycoplasma spp.* It is contemplated that the compounds of the invention can be used in combating and/or eliminating an infectious process caused by a microorganism in a host. In a particular aspect of the invention, the high potency and activity of these compounds make them attractive candidates for use in preventative therapies, such as sterilization of wounds prior to suture, as well as the sterilization of instruments prior to their use in surgical or other invasive procedures.

The invention is also directed to methods for treating a microbial infection in a host using a composition or compositions of the invention. For instance, the subject method can be used to treat or prevent nosocomial bacteremia and skin/wound infection, or lower respiratory infection, endocarditis, and infections of the urinary tract. According to the present invention, treatment of such bacterial diseases comprises the administration of a pharmaceutical composition of the invention in a therapeutically effective amount to an individual in need of such treatment. The compositions may be administered parenterally by intramuscular, intravenous, intraocular, intraperitoneal, or subcutaneous routes; inhalation; orally, topically and intranasally.

Their antimicrobial activity also renders the compounds of the invention particularly useful in inhibiting unwanted microbial growth in tissue culture, particularly those used for production of recombinant proteins or vectors for use in gene therapy.

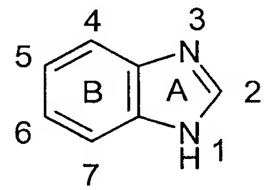
The invention is also directed to pharmaceutical compositions, comprising one or more of the antimicrobial compounds of the invention as the active ingredient(s), which may be administered to a host animal.

## *Definitions*

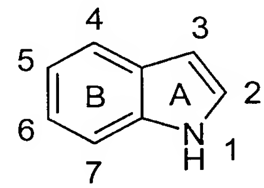
For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

The terms "benzimidazole" and “indole” are intended to mean compounds having the

following general chemical structures, wherein the numbers around their peripheries indicate the art-recognized positional designations for the two ring systems, and the capital letters contained within the individual rings are, likewise, their art-recognized descriptors. In both compounds, the B-rings may also be described as fused benzo rings.



*benzimidazole*



*indole*

An analog of a benzimidazole or indole is intended to mean any derivative of a benzimidazole or indole, in particular derivatives that adhere to the rules of valence in which a nitrogen is replaced by another atom, derivatives in which any of the carbon atoms are replaced with another heavy atom, and derivatives in which additional chemical groups are attached to any of the heavy atoms of the molecule.

The term "$ED_{50}$" means the dose of a drug which produces 50% of its maximum response or effect. Alternatively, the dose which produces a pre-determined response in 50% of test subjects or preparations.

The term "$LD_{50}$" means the dose of a drug which is lethal in 50% of test subjects.

The term "therapeutic index" refers to the therapeutic index of a drug defined as $LD_{50}/ED_{50}$.

The term "structure-activity relationship (SAR)" refers to the way in which altering the molecular structure of drugs alters their interaction with a receptor, enzyme, etc.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are boron, nitrogen, oxygen, phosphorus, sulfur and selenium.

The term "electron-withdrawing group" is recognized in the art, and denotes the tendency of a substituent to attract valence electrons from neighboring atoms, i.e., the substituent is electronegative with respect to neighboring atoms. A quantification of the level of electron-withdrawing capability is given by the Hammett sigma ($\sigma$) constant. This well known constant is described in many references, for instance, J. March, Advanced Organic Chemistry, McGraw Hill Book Company, New York, (1977 edition) pp. 251-259. The

Hammett constant values are generally negative for electron donating groups ($\sigma[P] = -0.66$ for $NH_2$) and positive for electron withdrawing groups ($\sigma[P] = 0.78$ for a nitro group), $\sigma[P]$ indicating para substitution. Exemplary electron-withdrawing groups include nitro, acyl, formyl, sulfonyl, trifluoromethyl, cyano, chloride, and the like. Exemplary electron-donating groups include amino, methoxy, and the like.

The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., $C_1$-$C_{30}$ for straight chain, $C_3$-$C_{30}$ for branched chain), and more preferably 20 or fewer. Likewise, preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 5, 6 or 7 carbons in the ring structure.

Moreover, the term "alkyl" (or "lower alkyl") as used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), $-CF_3$, -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, $-CF_3$, -CN, and the like.

The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. Preferred alkyl groups are lower alkyls. In preferred embodiments, a substituent designated herein as alkyl is a lower alkyl.

The term "aryl" as used herein includes 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, $-CF_3$, -CN, or the like. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.

The terms *ortho*, *meta* and *para* apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and *ortho*-dimethylbenzene are synonymous.

The terms "heterocyclyl" or "heterocyclic group" refer to 3- to 10-membered ring structures, more preferably 3- to 7-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can also be polycycles. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline,

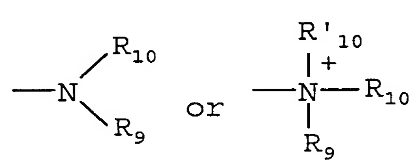
pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The terms "polycyclyl" or "polycyclic group" refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The term "carbocycle", as used herein, refers to an aromatic or non-aromatic ring in which each atom of the ring is carbon.

As used herein, the term "nitro" means $-NO_2$; the term "halogen" designates -F, -Cl, -Br or -I; the term "sulfhydryl" means -SH; the term "hydroxyl" means -OH; and the term "sulfonyl" means $-SO_2-$.

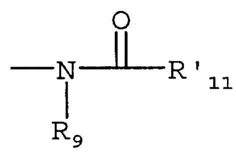
The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that can be represented by the general formula:



wherein $R_9$, $R_{10}$ and $R'_{10}$ each independently represent a hydrogen, an alkyl, an alkenyl, $-(CH_2)_m-R_8$, or $R_9$ and $R_{10}$ taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; $R_8$ represents an aryl, a

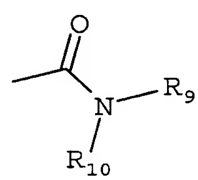
cycloalkyl, a cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In preferred embodiments, only one of $R_9$ or $R_{10}$ can be a carbonyl, e.g., $R_9$, $R_{10}$ and the nitrogen together do not form an imide. In even more preferred embodiments, $R_9$ and $R_{10}$ (and optionally $R'_{10}$) each independently represent a hydrogen, an alkyl, an alkenyl, or $-(CH_2)_m-R_8$. Thus, the term "alkylamine" as used herein means an amine group, as defined above, having a substituted or unsubstituted alkyl attached thereto, i.e., at least one of $R_9$ and $R_{10}$ is an alkyl group.

The term "acylamino" is art-recognized and refers to a moiety that can be represented by the general formula:



wherein $R_9$ is as defined above, and $R'_{11}$ represents a hydrogen, an alkyl, an alkenyl or $-(CH_2)_m-R_8$, where m and $R_8$ are as defined above.

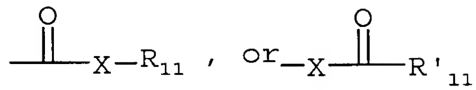
The term "amido" is art recognized as an amino-substituted carbonyl and includes a moiety that can be represented by the general formula:



wherein $R_9$, $R_{10}$ are as defined above. Preferred embodiments of the amide will not include imides which may be unstable.

The term "alkylthio" refers to an alkyl group, as defined above, having a sulfur radical attached thereto. In preferred embodiments, the "alkylthio" moiety is represented by one of -S-alkyl, -S-alkenyl, -S-alkynyl, and $-S-(CH_2)_m-R_8$, wherein m and $R_8$ are defined above. Representative alkylthio groups include methylthio, ethyl thio, and the like.

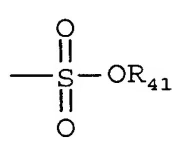
The term "carbonyl" is art recognized and includes such moieties as can be represented by the general formula:



wherein X is a bond or represents an oxygen or a sulfur, and $R_{11}$ represents a hydrogen, an alkyl, an alkenyl, $-(CH_2)_m-R_8$ or a pharmaceutically acceptable salt, $R'_{11}$ represents a hydrogen, an alkyl, an alkenyl or $-(CH_2)_m-R_8$, where m and $R_8$ are as defined above. Where X is an oxygen and $R_{11}$ or $R'_{11}$ is not hydrogen, the formula represents an "ester". Where X is an oxygen, and $R_{11}$ is as defined above, the moiety is referred to herein as a carboxyl group, and particularly when $R_{11}$ is a hydrogen, the formula represents a "carboxylic acid". Where X is an oxygen, and $R'_{11}$ is hydrogen, the formula represents a "formate". In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a "thiolcarbonyl" group. Where X is a sulfur and $R_{11}$ or $R'_{11}$ is not hydrogen, the formula represents a "thiolester." Where X is a sulfur and $R_{11}$ is hydrogen, the formula represents a "thiolcarboxylic acid." Where X is a sulfur and $R_{11}'$ is hydrogen, the formula represents a "thiolformate." On the other hand, where X is a bond, and $R_{11}$ is not hydrogen, the above formula represents a "ketone" group. Where X is a bond, and $R_{11}$ is hydrogen, the above formula represents an "aldehyde" group.

The terms "alkoxyl" or "alkoxy" as used herein refers to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as can be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, $-O-(CH_2)_m-R_8$, where m and $R_8$ are described above.

The term "sulfonate" is art recognized and includes a moiety that can be represented by the general formula:

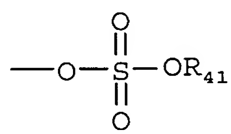


in which $R_{41}$ is an electron pair, hydrogen, alkyl, cycloalkyl, or aryl.

The terms triflyl, tosyl, mesyl, and nonaflyl are art-recognized and refer to trifluoromethanesulfonyl, *p*-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized and refer to trifluoromethanesulfonate ester, *p*-toluenesulfonate ester, methanesulfonate ester, and nonafluorobutanesulfonate ester functional groups and molecules that contain said groups, respectively.

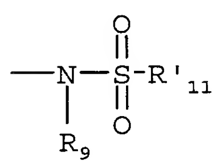
The abbreviations Me, Et, Ph, Tf, Nf, Ts, and Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, *p*-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry*; this list is typically presented in a table entitled Standard List of Abbreviations. The abbreviations contained in said list, and all abbreviations utilized by organic chemists of ordinary skill in the art are hereby incorporated by reference.

The term "sulfate" is art recognized and includes a moiety that can be represented by the general formula:



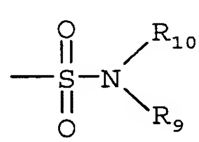
in which $R_{41}$ is as defined above.

The term "sulfonamido" is art recognized and includes a moiety that can be represented by the general formula:



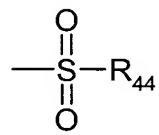
in which $R_9$ and $R'_{11}$ are as defined above.

The term "sulfamoyl" is art-recognized and includes a moiety that can be represented by the general formula:



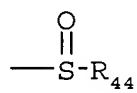
in which $R_9$ and $R_{10}$ are as defined above.

The term “sulfonyl”, as used herein, refers to a moiety that can be represented by the general formula:



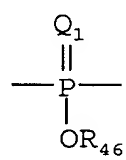
in which $R_{44}$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl.

The term "sulfoxido" as used herein, refers to a moiety that can be represented by the general formula:

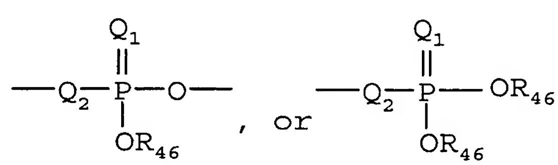


in which $R_{44}$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aralkyl, or aryl.

A "phosphoryl" can in general be represented by the formula:



wherein $Q_1$ represented S or O, and $R_{46}$ represents hydrogen, a lower alkyl or an aryl. When used to substitute, e.g., an alkyl, the phosphoryl group of the phosphorylalkyl can be represented by the general formula:



wherein $Q_1$ represented S or O, and each $R_{46}$ independently represents hydrogen, a lower alkyl or an aryl, $Q_2$ represents O, S or N. When $Q_1$ is an S, the phosphoryl moiety is a “phosphorothioate”.

A "selenoalkyl" refers to an alkyl group having a substituted seleno group attached

thereto. Exemplary "selenoethers" which may be substituted on the alkyl are selected from one of -Se-alkyl, -Se-alkenyl, -Se-alkynyl, and -Se-$(CH_2)_m$-$R_7$, m and $R_7$ being defined above.

Analogous substitutions can be made to alkenyl and alkynyl groups to produce, for example, aminoalkenyls, aminoalkynyls, amidoalkenyls, amidoalkynyls, iminoalkenyls, iminoalkynyls, thioalkenyls, thioalkynyls, carbonyl-substituted alkenyls or alkynyls.

As used herein, the definition of each expression, e.g. alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

The phrase "protecting group" as used herein means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991).

Certain compounds of the present invention may exist in particular geometric or

stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

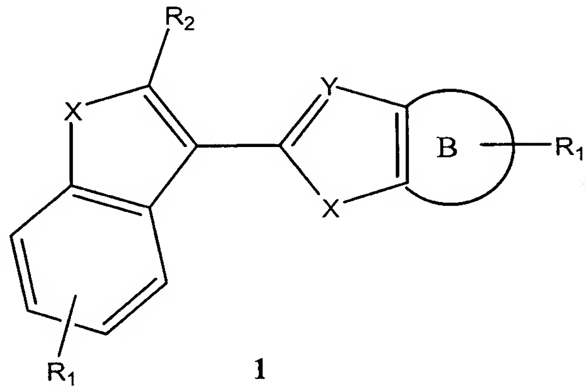
If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Contemplated equivalents of the compounds described above include compounds which otherwise correspond thereto, and which have the same general properties thereof (e.g., functioning as analgesics), wherein one or more simple variations of substituents are made which do not adversely affect the efficacy of the compound in binding to opioid receptors. In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are in themselves known, but are not mentioned here.

For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover. Also for purposes of this invention, the term "hydrocarbon" is contemplated to include all permissible compounds having at least one hydrogen and one carbon atom. In a broad aspect, the permissible hydrocarbons include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic organic compounds which can be substituted or unsubstituted.

*Compounds of the Invention.*

In certain embodiments, the compounds of the present invention are represented by generalized structure **1**:



**1**

wherein

X represents independently for each occurrence NR, O or S;

Y represents N or NO;

B represents a fused ring selected from the group consisting of monocyclic or polycyclic cycloalkyls, cycloalkenyls, aryls, heteroaryls, and heterocyclic rings, said rings comprising from 4 to 8 atoms in a ring structure;

R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, hydroxyl, alkoxyl, -$(CH_2)_n$Oalkyl, -$(CH_2)_n$Oaryl, formyl, acyl, -C(O)Oalkyl, -OC(O)Oaryl, -C(O)NHalkyl, -OC(O)NHaryl, alkylsulfonyl, -$(CH_2)_nC(O)N(R_{80})_2$, -$(CH_2)_n$-CH(OH)-$CH_2N(R_{80})_2$, or -$(CH_2)_n$-$R_{80}$;

B may be unsubstituted or substituted with $R_1$ any number of times up to the maximum number permitted by the structure of B;

the B-ring of the 1-X-bicyclo[4.3.0]nonatetradien-3-yl moiety may be unsubstituted or substituted with up to four instances of $R_1$;

$R_1$, when present, is selected independently for each occurrence from the set consisting of Me, lower alkyl, alkenyl, -C≡C-$R_{80}$, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, halogen, hydroxyl, alkoxyl, nitro, nitroso, cyano, acyl, acylamino, amido, alkoxycarbonyl, sulfonyl, sulfonamido, acyloxy, -$(CH_2)_nC(O)N(R_{80})_2$, -$(CH_2)_n$-CH(OH)-$CH_2N(R_{80})_2$, and -$(CH_2)_n$-$R_{80}$;

$R_2$ represents H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, hydroxyl, alkoxyl, -$(CH_2)_n$Oalkyl, -$(CH_2)_n$Oaryl, formyl, acyl, -C(O)Oalkyl, -OC(O)Oaryl, -C(O)NHalkyl, -OC(O)NHaryl, sulfonyl, -$(CH_2)_nC(O)N(R_{80})_2$, -$(CH_2)_n$-CH(OH)-$CH_2N(R_{80})_2$, or -$(CH_2)_n$-$R_{80}$;

$R_{80}$ represents independently for each occurrence H or an optionally substituted alkyl, acyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl moiety; and

n independently for each occurrence is an integer in the range 0 to 8 inclusive.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein B represents a fused aromatic or heteroaromatic ring.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein X represents NR.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein Y represents N.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein B represents a fused aromatic or heteroaromatic ring; and X represents NR.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein B represents a fused aromatic or heteroaromatic ring; and Y represents N.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein B represents a fused aromatic or heteroaromatic ring; and $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein B represents a fused aromatic or heteroaromatic ring; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein B represents a fused aromatic or heteroaromatic ring; X represents NR; and Y represents N.

In certain embodiments, the compounds of the present invention are represented by

generalized structure **1** and the attendant definitions, wherein B represents a fused aromatic or heteroaromatic ring; X represents NR; and $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein B represents a fused aromatic or heteroaromatic ring; Y represents N; and $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein B represents a fused aromatic or heteroaromatic ring; X represents NR; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein B represents a fused aromatic or heteroaromatic ring; Y represents N; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein B represents a fused aromatic or heteroaromatic ring; X represents NR; Y represents N; and $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein B represents a fused aromatic or heteroaromatic ring; X represents NR; Y represents N; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein B represents a fused aromatic or heteroaromatic ring; X represents NR; $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl; and $R_2$ is H, Me, or lower alkyl.

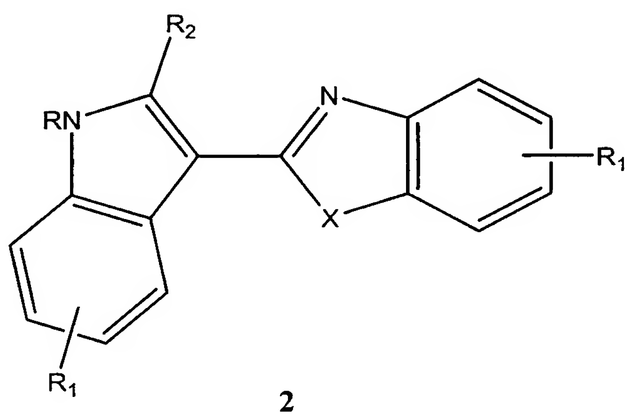
In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein B represents a fused aromatic or heteroaromatic ring; Y represents N; $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **1** and the attendant definitions, wherein B represents a fused aromatic or heteroaromatic ring; X represents NR; Y represents N; $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, compounds represented by generalized structure **1** display minimum inhibitory concentrations (MICs) below 25 μg/mL against certain Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus*, ciprofloxacin-resistant *Staphylococcus aureus*, and/or *Streptococcus pneumoniae*. In more preferred embodiments, the compounds have MIC values less than 10 μg/mL or even less than 1 μg/mL against such bacteria, particularly against methicillin-resistant *Staphylococcus aureus* or ciprofloxacin-resistant *Staphylococcus aureus* or both.

In certain embodiments, compounds represented by generalized structure **1** display minimum inhibitory concentrations (MICs) below 25 μg/mL against certain Gram-negative bacteria. In more preferred embodiments, the compounds have MIC values less than 10 μg/mL or even less than 1 μg/mL against such bacteria.

In certain embodiments, the compounds of the present invention are represented by generalized structure **2**:




**2**

wherein

X represents NR, O or S;

R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, hydroxyl, alkoxyl, -$(CH_2)_n$Oalkyl, -$(CH_2)_n$Oaryl, formyl, acyl, -C(O)Oalkyl, -OC(O)Oaryl, -C(O)NHalkyl, -OC(O)NHaryl, alkylsulfonyl, -$(CH_2)_nC(O)N(R_{80})_2$, -$(CH_2)_n$-CH(OH)-$CH_2N(R_{80})_2$, or -$(CH_2)_n$-$R_{80}$;

$R_1$ independently for each occurrence is absent or present between one and four times on each fused benzo ring;

$R_1$, when present, is selected independently for each occurrence from the set consisting of Me, lower alkyl, alkenyl, -C≡C-$R_{80}$, lower heteroalkyl, aryl, heteroaryl, aralkyl,

heteroaralkyl, cycloalkyl, heterocycloalkyl, halogen, hydroxyl, alkoxyl, nitro, nitroso, cyano, acyl, acylamino, amido, alkoxycarbonyl, sulfonyl, sulfonamido, acyloxy, $-(CH_2)_nC(O)N(R_{80})_2$, $-(CH_2)_n-CH(OH)-CH_2N(R_{80})_2$, and $-(CH_2)_n-R_{80}$;

$R_2$ represents H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, hydroxyl, alkoxyl, $-(CH_2)_n$Oalkyl, $-(CH_2)_n$Oaryl, formyl, acyl, -C(O)Oalkyl, -OC(O)Oaryl, -C(O)NHalkyl, -OC(O)NHaryl, sulfonyl, $-(CH_2)_nC(O)N(R_{80})_2$, $-(CH_2)_n-CH(OH)-CH_2N(R_{80})_2$, or $-(CH_2)_n-R_{80}$;

$R_{80}$ represents independently for each occurrence H or an optionally substituted alkyl, acyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl moiety; and

n independently for each occurrence is an integer in the range 0 to 8 inclusive.

In certain embodiments, the compounds of the present invention are represented by generalized structure **2** and the attendant definitions, wherein X represents NR.

In certain embodiments, the compounds of the present invention are represented by generalized structure **2** and the attendant definitions, wherein $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **2** and the attendant definitions, wherein $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **2** and the attendant definitions, wherein X represents NR; and $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **2** and the attendant definitions, wherein X represents NR; and $R_2$ is H, Me, or lower alkyl.

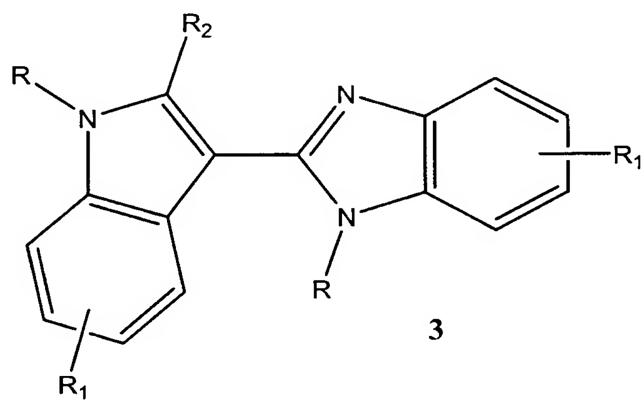
In certain embodiments, the compounds of the present invention are represented by generalized structure **2** and the attendant definitions, wherein $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **2** and the attendant definitions, wherein X represents NR; $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, compounds represented by generalized structure **2** display minimum inhibitory concentrations (MICs) below 25 μg/mL against certain Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus*, ciprofloxacin-resistant *Staphylococcus aureus*, and/or *Streptococcus pneumoniae*. In more preferred embodiments, the compounds have MIC values less than 10 μg/mL or even less than 1 μg/mL against such bacteria, particularly against methicillin-resistant *Staphylococcus aureus* or ciprofloxacin-resistant *Staphylococcus aureus* or both.

In certain embodiments, compounds represented by generalized structure **2** display minimum inhibitory concentrations (MICs) below 25 μg/mL against certain Gram-negative bacteria. In more preferred embodiments, the compounds have MIC values less than 10 μg/mL or even less than 1 μg/mL against such bacteria.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3**:



**3**

wherein

R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, hydroxyl, alkoxyl, $-(CH_2)_nO$alkyl, $-(CH_2)_nO$aryl, formyl, acyl, -C(O)Oalkyl, -OC(O)Oaryl, -C(O)NHalkyl, -OC(O)NHaryl, alkylsulfonyl, $-(CH_2)_nC(O)N(R_{80})_2$, $-(CH_2)_n-CH(OH)-CH_2N(R_{80})_2$, or $-(CH_2)_n-R_{80}$;

$R_1$ independently for each occurrence is absent or present between one and four times on each fused benzo ring;

$R_1$, when present, is selected independently for each occurrence from the set consisting of Me, lower alkyl, alkenyl, $-C\equiv C-R_{80}$, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, halogen, hydroxyl, alkoxyl, nitro, nitroso, cyano, acyl, acylamino, amido, alkoxycarbonyl, sulfonyl, sulfonamido, acyloxy, $-(CH_2)_nC(O)N(R_{80})_2$, $-(CH_2)_n-CH(OH)-CH_2N(R_{80})_2$, and $-(CH_2)_n-R_{80}$;

$R_2$ represents H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, hydroxyl, alkoxyl, -$(CH_2)_n$Oalkyl, -$(CH_2)_n$Oaryl, formyl, acyl, -C(O)Oalkyl, -OC(O)Oaryl, -C(O)NHalkyl, -OC(O)NHaryl, sulfonyl, -$(CH_2)_n$C(O)N$(R_{80})_2$, -$(CH_2)_n$-CH(OH)-$CH_2$N$(R_{80})_2$, or -$(CH_2)_n$-$R_{80}$;

$R_{80}$ represents independently for each occurrence H or an optionally substituted alkyl, acyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl moiety; and

n independently for each occurrence is an integer in the range 0 to 8 inclusive.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein $R_1$ is present at least once on the B-ring of the indolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein $R_1$ is present at least once on the B-ring of the indolyl moiety; and said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein $R_1$ is present exactly once on the B-ring of the indolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein $R_1$ is present exactly once on the B-ring of the indolyl moiety; and said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein $R_1$ is present once or twice on

the B-ring of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; and $R_1$ is present at least once on the B-ring of the indolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; and said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; and $R_1$ is present exactly once on the B-ring of the indolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; and said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; and $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl,

heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; and $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; and $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; and $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for

each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; and $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; and $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; and $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by

generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; and $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; and $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; and $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety.

In certain embodiments, the compounds of the present invention are represented by

generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the

benzimidazolyl moiety; said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; said

instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and $R_2$

is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for

each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, the compounds of the present invention are represented by generalized structure **3** and the attendant definitions, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both; and $R_2$ is H, Me, or lower alkyl.

In certain embodiments, compounds represented by generalized structure **3** display minimum inhibitory concentrations (MICs) below 25 μg/mL against certain Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus*, ciprofloxacin-resistant *Staphylococcus aureus*, and/or *Streptococcus pneumoniae*. In more preferred embodiments, the compounds have MIC values less than 10 μg/mL or even less than 1 μg/mL against such bacteria, particularly against methicillin-resistant *Staphylococcus aureus* or ciprofloxacin-resistant *Staphylococcus aureus* or both.

In certain embodiments, compounds represented by generalized structure **3** display minimum inhibitory concentrations (MICs) below 25 μg/mL against certain Gram-negative bacteria. In more preferred embodiments, the compounds have MIC values less than 10 μg/mL or even less than 1 μg/mL against such bacteria.

In certain embodiments, the present invention relates to a pharmaceutical preparation, comprising a compound represented by **1**, **2**, or **3**, and any of the attendant sets of definitions; and a pharmaceutically acceptable excipient. In certain embodiments, the present invention relates to a disinfectant preparation, comprising a compound represented by **1**, **2**, or **3**, and any of the attendant sets of definitions.

In certain embodiments, the present invention relates to a method of treating a mammal suffering from a bacterial infection, comprising the step of:

administering to a mammal suffering from a bacterial infection a compound represented by **1**, **2**, or **3**, and any of the attendant sets of definitions, or a pharmaceutical preparation thereof.

In certain embodiments, the present invention relates to a method of treating a mammal suffering from a bacterial infection, comprising the steps of:

administering to a mammal suffering from a bacterial infection a compound represented by **1**, **2**, or **3**, and any of the attendant sets of definitions, or a pharmaceutical preparation thereof,; and

repeating said administration of said compound or preparation until said bacterial infection can no longer be detected in said mammal.

*Pharmaceutical Compositions*

In another aspect, the present invention provides pharmaceutically acceptable compositions which comprise a therapeutically-effective amount of one or more of the compounds described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or suspension; (3) topical application, for example, as a cream, ointment or spray applied to the skin; or (4) intravaginally or intrarectally, for example, as a pessary, cream or foam.

The phrase "therapeutically-effective amount" as used herein means that amount of a compound, material, or composition comprising a compound of the present invention which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the

body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

As set out above, certain embodiments of the present compounds may contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable acids. The term "pharmaceutically-acceptable salts" in this respect, refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19)

The pharmaceutically acceptable salts of the subject compounds include the conventional nontoxic salts or quaternary ammonium salts of the compounds, e.g., from non-toxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloride, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicyclic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable bases. The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of

compounds of the present invention. These salts can likewise be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically-acceptable metal cation, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge et al., *supra*)

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of

capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable

medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical

form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given in forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administrations are preferred.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

These compounds may be administered to humans and other animals for therapy by

any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous, intracerebroventricular and subcutaneous doses of the compounds of this invention for a patient, when used for the indicated analgesic effects, will range from about 0.0001 to about 100 mg per kilogram of body weight per day.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition).

In another aspect, the present invention provides pharmaceutically acceptable compositions which comprise a therapeutically-effective amount of one or more of the

subject co,pounds, as described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or suspension; (3) topical application, for example, as a cream, ointment or spray applied to the skin; or (4) intravaginally or intravectally, for example, as a pessary, cream or foam.

The compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other pharmaceuticals.

The term "treatment" is intended to encompass also prophylaxis, therapy and cure.

The patient receiving this treatment is any animal in need, including primates, in particular humans, and other mammals such as equines, cattle, swine and sheep; and poultry and pets in general.

The compound of the invention can be administered as such or in admixtures with pharmaceutically acceptable carriers and can also be administered in conjunction with antimicrobial agents such as penicillins, cephalosporins, aminoglycosides and glycopeptides. Conjunctive therapy, thus includes sequential, simultaneous and separate administration of the active compound in a way that the therapeutical effects of the first administered one is not entirely disappeared when the subsequent is administered.

The addition of the active compound of the invention to animal feed is preferably accomplished by preparing an appropriate feed premix containing the active compound in an effective amount and incorporating the premix into the complete ration.

Alternatively, an intermediate concentrate or feed supplement containing the active ingredient can be blended into the feed. The way in which such feed premixes and complete rations can be prepared and administered are described in reference books (such as "Applied Animal Nutrition", W.H. Freedman and Co., San Francisco, U.S.A., 1969 or "Livestock Feeds and Feeding" O and B books, Corvallis, OR, U.S.A., 1977).

*Combinatorial Libraries*

Diverse libraries of compounds of the present invention may be synthesized via the methods of combinatorial synthesis. These combinatorial libraries of the compounds will enable their rapid, high-throughput screening for pharmaceutical, agrochemical or other

biological or medically-related activity or material-related qualities. For the purposes of the present invention, a combinatorial library is a mixture of chemically related compounds which may be screened together for a desired property; said libraries may be in solution or covalently linked to a solid support. The preparation of many related compounds in a single reaction greatly reduces the number of purification steps associated with the synthesizing the compounds, and also enables the initial screening of many compounds simultaneously. Screening for the appropriate biological, pharmaceutical, agrochemical or physical property may be done by conventional methods.

Diversity in a library can be created at a variety of different levels. For example, the reactants used in a combinatorial synthesis approach can be diverse in terms of their ring structures or in terms of substitution thereof or both.

A variety of techniques are available in the art for generating combinatorial libraries of small organic molecules. See, for example, Blondelle et al. (1995) Trends Anal. Chem. 14:83; the Affymax U.S. Patents 5,359,115 and 5,362,899: the Ellman U.S. Patent 5,288,514: the Still et al. PCT publication WO 94/08051; Chen et al. (1994) JACS 116:2661: Kerr et al. (1993) JACS 115:252; PCT publications WO92/10092, WO93/09668 and WO91/07087; and the Lerner et al. PCT publication WO93/20242). Accordingly, a variety of libraries on the order of about 16 to 1,000,000 or more compounds (so-called "diversomers") can be synthesized and screened for a particular activity or property.

In an exemplary embodiment, a library of substituted diversomers can be synthesized according to the techniques described in the Still et al. PCT publication WO 94/08051, e.g., being linked to a polymer bead by a hydrolyzable or photolyzable group, e.g., located at one of the positions of substrate. According to the Still et al. technique, the library is synthesized on a set of beads, each bead including a set of tags identifying the particular diversomer on that bead. In one embodiment, which is particularly suitable for discovering enzyme inhibitors, the beads can be dispersed on the surface of a permeable membrane, and the diversomers released from the beads by lysis of the bead linker. The diversomer from each bead will diffuse across the membrane to an assay zone, where it will interact with an enzyme assay. Detailed descriptions of a number of combinatorial methodologies are provided below.

A) Direct Characterization

A growing trend in the field of combinatorial chemistry is to exploit the sensitivity of techniques such as mass spectrometry (MS), e.g., which can be used to characterize sub-femtomolar amounts of a compound, and to directly determine the chemical constitution of a compound selected from a combinatorial library. For instance, where the library is provided on an insoluble support matrix, discrete populations of compounds can be first released from the support and characterized by MS. In other embodiments, as part of the MS sample

preparation technique, such MS techniques as MALDI can be used to release a compound from the matrix, particularly where a labile bond is used originally to tether the compound to the matrix. For instance, a bead selected from a library can be irradiated in a MALDI step in order to release the diversomer from the matrix, and ionize the diversomer for MS analysis.

B) Multipin Synthesis

The libraries of the subject method can take the multipin library format. Briefly, Geysen and co-workers (Geysen et al. (1984) PNAS 81:3998-4002) introduced a method for generating compound libraries by a parallel synthesis on polyacrylic acid-grated polyethylene pins arrayed in the microtitre plate format. The Geysen technique can be used to synthesize and screen thousands of compounds per week using the multipin method, and the tethered compounds may be reused in many assays. Appropriate linker moieties can also been appended to the pins so that the compounds may be cleaved from the supports after synthesis for assessment of purity and further evaluation (c.f., Bray et al. (1990) Tetrahedron Lett 31:5811-5814; Valerio et al. (1991) Anal Biochem 197:168-177; Bray et al. (1991) Tetrahedron Lett 32:6163-6166).

C) Divide-Couple-Recombine

In yet another embodiment, a variegated library of compounds can be provided on a set of beads utilizing the strategy of divide-couple-recombine (see, e.g., Houghten (1985) PNAS 82:5131-5135; and U.S. Patents 4,631,211; 5,440,016; 5,480,971). Briefly, as the name implies, at each synthesis step where degeneracy is introduced into the library, the beads are divided into separate groups equal to the number of different substituents to be added at a particular position in the library, the different substituents coupled in separate reactions, and the beads recombined into one pool for the next iteration.

In one embodiment, the divide-couple-recombine strategy can be carried out using an analogous approach to the so-called "tea bag" method first developed by Houghten, where compound synthesis occurs on resin sealed inside porous polypropylene bags (Houghten et al. (1986) PNAS 82:5131-5135). Substituents are coupled to the compound-bearing resins by placing the bags in appropriate reaction solutions, while all common steps such as resin washing and deprotection are performed simultaneously in one reaction vessel. At the end of the synthesis, each bag contains a single compound.

D) Combinatorial Libraries by Light-Directed, Spatially Addressable Parallel Chemical Synthesis

A scheme of combinatorial synthesis in which the identity of a compound is given by its locations on a synthesis substrate is termed a spatially-addressable synthesis. In one embodiment, the combinatorial process is carried out by controlling the addition of a chemical reagent to specific locations on a solid support (Dower et al. (1991) Annu Rep Med

Chem 26:271-280; Fodor, S.P.A. (1991) Science 251:767; Pirrung et al. (1992) U.S. Patent No. 5,143,854; Jacobs et al. (1994) Trends Biotechnol 12:19-26). The spatial resolution of photolithography affords miniaturization. This technique can be carried out through the use protection/deprotection reactions with photolabile protecting groups.

The key points of this technology are illustrated in Gallop et al. (1994) J Med Chem 37:1233-1251. A synthesis substrate is prepared for coupling through the covalent attachment of photolabile nitroveratryloxycarbonyl (NVOC) protected amino linkers or other photolabile linkers. Light is used to selectively activate a specified region of the synthesis support for coupling. Removal of the photolabile protecting groups by light (deprotection) results in activation of selected areas. After activation, the first of a set of amino acid analogs, each bearing a photolabile protecting group on the amino terminus, is exposed to the entire surface. Coupling only occurs in regions that were addressed by light in the preceding step. The reaction is stopped, the plates washed, and the substrate is again illuminated through a second mask, activating a different region for reaction with a second protected building block. The pattern of masks and the sequence of reactants define the products and their locations. Since this process utilizes photolithography techniques, the number of compounds that can be synthesized is limited only by the number of synthesis sites that can be addressed with appropriate resolution. The position of each compound is precisely known; hence, its interactions with other molecules can be directly assessed.

In a light-directed chemical synthesis, the products depend on the pattern of illumination and on the order of addition of reactants. By varying the lithographic patterns, many different sets of test compounds can be synthesized simultaneously; this characteristic leads to the generation of many different masking strategies.

E) Encoded Combinatorial Libraries

In yet another embodiment, the subject method utilizes a compound library provided with an encoded tagging system. A recent improvement in the identification of active compounds from combinatorial libraries employs chemical indexing systems using tags that uniquely encode the reaction steps a given bead has undergone and, by inference, the structure it carries. Conceptually, this approach mimics phage display libraries, where activity derives from expressed peptides, but the structures of the active peptides are deduced from the corresponding genomic DNA sequence. The first encoding of synthetic combinatorial libraries employed DNA as the code. A variety of other forms of encoding have been reported, including encoding with sequenceable bio-oligomers (e.g., oligonucleotides and peptides), and binary encoding with additional non-sequenceable tags.

1) Tagging with sequenceable bio-oligomers

The principle of using oligonucleotides to encode combinatorial synthetic libraries was described in 1992 (Brenner et al. (1992) PNAS 89:5381-5383), and an example

of such a library appeared the following year (Needles et al. (1993) PNAS 90:10700-10704). A combinatorial library of nominally $7^7$ (= 823,543) peptides composed of all combinations of Arg, Gln, Phe, Lys, Val, D-Val and Thr (three-letter amino acid code), each of which was encoded by a specific dinucleotide (TA, TC, CT, AT, TT, CA and AC, respectively), was prepared by a series of alternating rounds of peptide and oligonucleotide synthesis on solid support. In this work, the amine linking functionality on the bead was specifically differentiated toward peptide or oligonucleotide synthesis by simultaneously preincubating the beads with reagents that generate protected OH groups for oligonucleotide synthesis and protected $NH_2$ groups for peptide synthesis (here, in a ratio of 1:20). When complete, the tags each consisted of 69-mers, 14 units of which carried the code. The bead-bound library was incubated with a fluorescently labeled antibody, and beads containing bound antibody that fluoresced strongly were harvested by fluorescence-activated cell sorting (FACS). The DNA tags were amplified by PCR and sequenced, and the predicted peptides were synthesized. Following such techniques, compound libraries can be derived for use in the subject method, where the oligonucleotide sequence of the tag identifies the sequential combinatorial reactions that a particular bead underwent, and therefore provides the identity of the compound on the bead.

The use of oligonucleotide tags permits exquisitely sensitive tag analysis. Even so, the method requires careful choice of orthogonal sets of protecting groups required for alternating co-synthesis of the tag and the library member. Furthermore, the chemical lability of the tag, particularly the phosphate and sugar anomeric linkages, may limit the choice of reagents and conditions that can be employed for the synthesis of non-oligomeric libraries. In preferred embodiments, the libraries employ linkers permitting selective detachment of the test compound library member for assay.

Peptides have also been employed as tagging molecules for combinatorial libraries. Two exemplary approaches are described in the art, both of which employ branched linkers to solid phase upon which coding and ligand strands are alternately elaborated. In the first approach (Kerr JM et al. (1993) J Am Chem Soc 115:2529-2531), orthogonality in synthesis is achieved by employing acid-labile protection for the coding strand and base-labile protection for the compound strand.

In an alternative approach (Nikolaiev et al. (1993) Pept Res 6:161-170), branched linkers are employed so that the coding unit and the test compound can both be attached to the same functional group on the resin. In one embodiment, a cleavable linker can be placed between the branch point and the bead so that cleavage releases a molecule containing both code and the compound (Ptek et al. (1991) Tetrahedron Lett 32:3891-3894). In another embodiment, the cleavable linker can be placed so that the test compound can be selectively separated from the bead, leaving the code behind. This last construct is particularly valuable because it permits screening of the test compound without potential

interference of the coding groups. Examples in the art of independent cleavage and sequencing of peptide library members and their corresponding tags has confirmed that the tags can accurately predict the peptide structure.

2) Non-sequenceable Tagging: Binary Encoding

An alternative form of encoding the test compound library employs a set of non-sequencable electrophoric tagging molecules that are used as a binary code (Ohlmeyer et al. (1993) PNAS 90:10922-10926). Exemplary tags are haloaromatic alkyl ethers that are detectable as their trimethylsilyl ethers at less than femtomolar levels by electron capture gas chromatography (ECGC). Variations in the length of the alkyl chain, as well as the nature and position of the aromatic halide substituents, permit the synthesis of at least 40 such tags, which in principle can encode $2^{40}$ (e.g., upwards of $10^{12}$) different molecules. In the original report (Ohlmeyer et al., supra) the tags were bound to about 1% of the available amine groups of a peptide library via a photocleavable o-nitrobenzyl linker. This approach is convenient when preparing combinatorial libraries of peptide-like or other amine-containing molecules. A more versatile system has, however, been developed that permits encoding of essentially any combinatorial library. Here, the compound would be attached to the solid support via the photocleavable linker and the tag is attached through a catechol ether linker via carbene insertion into the bead matrix (Nestler et al. (1994) J Org Chem 59:4723-4724). This orthogonal attachment strategy permits the selective detachment of library members for assay in solution and subsequent decoding by ECGC after oxidative detachment of the tag sets.

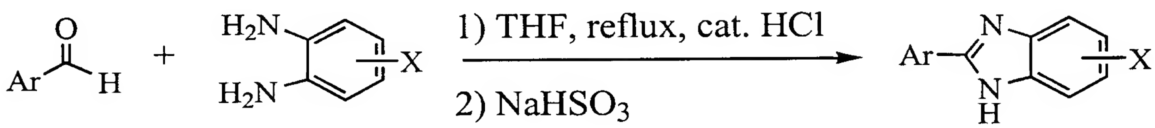
Although several amide-linked libraries in the art employ binary encoding with the electrophoric tags attached to amine groups, attaching these tags directly to the bead matrix provides far greater versatility in the structures that can be prepared in encoded combinatorial libraries. Attached in this way, the tags and their linker are nearly as unreactive as the bead matrix itself. Two binary-encoded combinatorial libraries have been reported where the electrophoric tags are attached directly to the solid phase (Ohlmeyer et al. (1995) PNAS 92:6027-6031) and provide guidance for generating the subject compound library. Both libraries were constructed using an orthogonal attachment strategy in which the library member was linked to the solid support by a photolabile linker and the tags were attached through a linker cleavable only by vigorous oxidation. Because the library members can be repetitively partially photoeluted from the solid support, library members can be utilized in multiple assays. Successive photoelution also permits a very high throughput iterative screening strategy: first, multiple beads are placed in 96-well microtiter plates; second, compounds are partially detached and transferred to assay plates; third, a metal binding assay identifies the active wells; fourth, the corresponding beads are rearrayed singly into new microtiter plates; fifth, single active compounds are identified; and sixth, the structures are decoded.

### *Exemplification*

The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

## *Example 1*

General Procedures for Preparation of Aryl-Benzimidazoles



A B C

Aromatic aldehyde **A** (3.3 mmol) and phenylene diamine **B** (3 mmol) were dissolved in 50 mL of dry THF. Two drops of a 4 N solution of HCl in dioxane was then added. The solution was heated to a gentle reflux. After 30 minutes at reflux, an aqueous solution of sodium bisulfite (9 mL of a 1M solution; 9 mmol) was added. After overnight reflux, the solution was cooled to room temperature, diluted with 150 mL of ethyl acetate, and the mixture was washed with water and brine. The organic layer was then concentrated *in vacuo*. The residue was resuspended in methylene chloride. Any insoluble material present was removed via filtration and identified as the aryl-benzimidazole product **C**. If no insoluble material was present the mixture was purified by flash chromatography on silica gel, typically using a gradient elution with ethyl acetate-hexane. The aryl-benzimidazole product typically exhibited polarity on silica gel similar to the starting phenylene diamine **A**. The aryl-benzimidazole product **C** was typically isolated in 30-70% chemical yield based on **B**.

In certain instances, the aryl-benzimidazole product **C** could be obtained from **A** and **B** in greater purity and/or yield by following a second procedure. A slurry of powdered $NaHSO_3$ (4 equiv) and equimolar quantities of **A** and **B** in anhydrous DMF was heated at 120 C for 8-24 h. The reaction mixture was allowed to cool to room temperature, and was diluted with 150 mL of ethyl acetate. The resulting mixture was washed with water and brine, and the organic layer was concentrated *in vacuo*. The residue was resuspended in methylene chloride, and purified as outlined in the preceding paragraph to give aryl-benzimidazole product **C**.

***Example 2***

Determination of MIC Values for Aryl-Benzimidazoles

Stock solutions of compounds are prepared with a concentration of 10 mg/mL. These solutions are then diluted 1:4 to give a concentration of 2.5 mg/mL. The compounds are then serially diluted 1:2 for 6 iterations. The concentrations made for each compound are 2.5, 1.25, 0.625, 0.3125, 0.156, 0.078, and 0.039 mg/mL. A control sample (no compound) is run along with each compound tested. All dilutions are made in DMSO.

All wells of a 96 well microtiter plate are filled with 100 μL of BHI (Brain-Heart Infusion) broth. Columns on the plate are labeled 1-12, and rows are labeled A-H. Each column of wells is used to test one series of diluted compounds. Into each well of 100 μL of BHI broth, 1 μL of diluted compound is placed for a 1:100 dilution. This makes the final concentration of each drug series 25, 12.5, 6.25, 3.125, 1.56, 0.78, 0.39, and 0 μg/mL.

Next, a sterile 15 mL screw cap tube is filled wth 3 mL of BHI broth. Then, 2 or 3 colonies of test organism are inoculated into the tube. The tube is then incubated at 37 °C in a $CO_2$ (approx. 7%) atmosphere jar. The organisms are allowed to grow to a density of a 0.5 McFarland standard ($10^8$ cells/mL). The organism is then inoculated into each well of the microtiter plate containing the diluted compounds to be tested for MIC. The inoculum is 1 μL in volume and represents $10^5$ to $10^6$ cells/mL.

After inoculation of the wells of the microtiter plates, the plates are covered and incubated at 37 °C under ~7-10% $CO_2$ atmosphere overnight (about 16 hours). The plates are then observed for growth, the well with the lowest concentration of drug and no observable growth determines the MIC.

### *Incorporation By Reference*

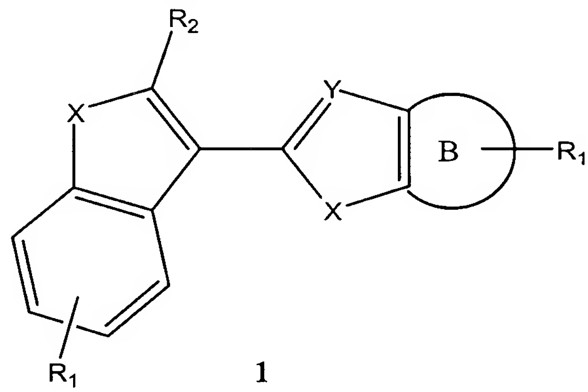
All of the patents and publications cited herein are hereby incorporated by reference.

### *Equivalents*

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

1. A compound represented by generalized structure **1**:



**1**

wherein

X represents independently for each occurrence NR, O or S;

Y represents N or NO;

B represents a fused ring selected from the group consisting of monocyclic or polycyclic cycloalkyls, cycloalkenyls, aryls, heteroaryls, and heterocyclic rings, said rings comprising from 4 to 8 atoms in a ring structure;

R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, hydroxyl, alkoxyl, -$(CH_2)_n$Oalkyl, -$(CH_2)_n$Oaryl, formyl, acyl, -C(O)Oalkyl, -OC(O)Oaryl, -C(O)NHalkyl, -OC(O)NHaryl, alkylsulfonyl, -$(CH_2)_n$C(O)N$(R_{80})_2$, -$(CH_2)_n$-CH(OH)-$CH_2$N$(R_{80})_2$, or -$(CH_2)_n$-$R_{80}$;

B may be unsubstituted or substituted with $R_1$ any number of times up to the maximum number permitted by the structure of B;

the B-ring of the 1-X-bicyclo[4.3.0]nonatetradien-3-yl moiety may be unsubstituted or substituted with up to four instances of $R_1$;

$R_1$, when present, is selected independently for each occurrence from the set consisting of Me, lower alkyl, alkenyl, -C≡C-$R_{80}$, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, halogen, hydroxyl, alkoxyl, nitro, nitroso, cyano, acyl, acylamino, amido, alkoxycarbonyl, sulfonyl, sulfonamido, acyloxy, -$(CH_2)_n$C(O)N$(R_{80})_2$, -$(CH_2)_n$-CH(OH)-$CH_2$N$(R_{80})_2$, and -$(CH_2)_n$-$R_{80}$;

$R_2$ represents H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, hydroxyl, alkoxyl, -$(CH_2)_n$Oalkyl, -$(CH_2)_n$Oaryl, formyl, acyl, -C(O)Oalkyl, -OC(O)Oaryl, -C(O)NHalkyl, -OC(O)NHaryl, sulfonyl, -$(CH_2)_n$C(O)N$(R_{80})_2$, -$(CH_2)_n$-CH(OH)-$CH_2$N$(R_{80})_2$, or -$(CH_2)_n$-$R_{80}$;

$R_{80}$ represents independently for each occurrence H or an optionally substituted alkyl, acyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl moiety; and

n independently for each occurrence is an integer in the range 0 to 8 inclusive.

2. The compound of claim 1, wherein B represents a fused aromatic or heteroaromatic ring.

3. The compound of claim 1, wherein X represents NR.

4. The compound of claim 1, wherein Y represents N.

5. The compound of claim 1, wherein $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl.

6. The compound of claim 1, wherein $R_2$ is H, Me, or lower alkyl.

7. The compound of claim 1, wherein B represents a fused aromatic or heteroaromatic ring; and X represents NR.

8. The compound of claim 1, wherein B represents a fused aromatic or heteroaromatic ring; and Y represents N.

9. The compound of claim 1, wherein B represents a fused aromatic or heteroaromatic ring; and $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl.

10. The compound of claim 1, wherein B represents a fused aromatic or heteroaromatic ring; and $R_2$ is H, Me, or lower alkyl.

11. The compound of claim 1, wherein B represents a fused aromatic or heteroaromatic ring; X represents NR; and Y represents N.

12. The compound of claim 1, wherein B represents a fused aromatic or heteroaromatic ring; X represents NR; and $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl.

13. The compound of claim 1, wherein B represents a fused aromatic or heteroaromatic ring; Y represents N; and $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl.

14. The compound of claim 1, wherein B represents a fused aromatic or heteroaromatic ring; X represents NR; and $R_2$ is H, Me, or lower alkyl.

15. The compound of claim 1, wherein B represents a fused aromatic or heteroaromatic ring; Y represents N; and $R_2$ is H, Me, or lower alkyl.

16. The compound of claim 1, wherein B represents a fused aromatic or heteroaromatic ring; X represents NR; Y represents N; and $R_1$ independently for each occurrence is

absent or selected from the group consisting of halogen, amido and alkoxycarbonyl.

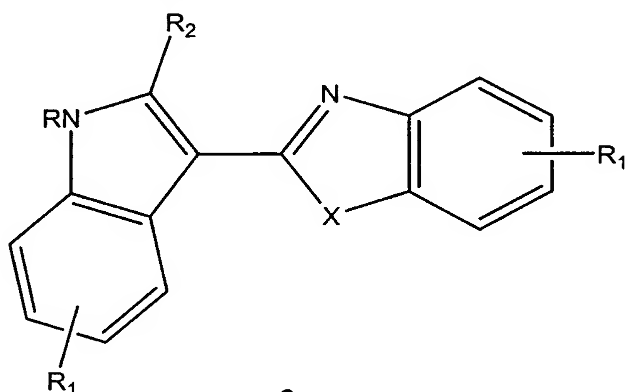
17. The compound of claim 1, wherein B represents a fused aromatic or heteroaromatic ring; X represents NR; Y represents N; and $R_2$ is H, Me, or lower alkyl.

18. The compound of claim 1, wherein B represents a fused aromatic or heteroaromatic ring; X represents NR; $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl; and $R_2$ is H, Me, or lower alkyl.

19. The compound of claim 1, wherein B represents a fused aromatic or heteroaromatic ring; Y represents N; $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl; and $R_2$ is H, Me, or lower alkyl.

20. The compound of claim 1, wherein B represents a fused aromatic or heteroaromatic ring; X represents NR; Y represents N; $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl; and $R_2$ is H, Me, or lower alkyl.

21. A compound represented by generalized structure **2**:




**2**

wherein

X represents NR, O or S;

R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, hydroxyl, alkoxyl, $-(CH_2)_n$Oalkyl, $-(CH_2)_n$Oaryl, formyl, acyl, -C(O)Oalkyl, -OC(O)Oaryl, -C(O)NHalkyl, -OC(O)NHaryl, alkylsulfonyl, $-(CH_2)_nC(O)N(R_{80})_2$, $-(CH_2)_n$-CH(OH)-$CH_2N(R_{80})_2$, or $-(CH_2)_n$-$R_{80}$;

$R_1$ independently for each occurrence is absent or present between one and four times on each fused benzo ring;

$R_1$, when present, is selected independently for each occurrence from the set

consisting of Me, lower alkyl, alkenyl, -C≡C-$R_{80}$, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, halogen, hydroxyl, alkoxyl, nitro, nitroso, cyano, acyl, acylamino, amido, alkoxycarbonyl, sulfonyl, sulfonamido, acyloxy, -$(CH_2)_nC(O)N(R_{80})_2$, -$(CH_2)_n$-CH(OH)-$CH_2N(R_{80})_2$, and -$(CH_2)_n$-$R_{80}$;

$R_2$ represents H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, hydroxyl, alkoxyl, -$(CH_2)_n$Oalkyl, -$(CH_2)_n$Oaryl, formyl, acyl, -C(O)Oalkyl, -OC(O)Oaryl, -C(O)NHalkyl, -OC(O)NHaryl, sulfonyl, -$(CH_2)_nC(O)N(R_{80})_2$, -$(CH_2)_n$-CH(OH)-$CH_2N(R_{80})_2$, or -$(CH_2)_n$-$R_{80}$;

$R_{80}$ represents independently for each occurrence H or an optionally substituted alkyl, acyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl moiety; and

n independently for each occurrence is an integer in the range 0 to 8 inclusive.

22. The compound of claim 21, wherein X represents NR.

23. The compound of claim 21, wherein $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl.

24. The compound of claim 21, wherein $R_2$ is H, Me, or lower alkyl.

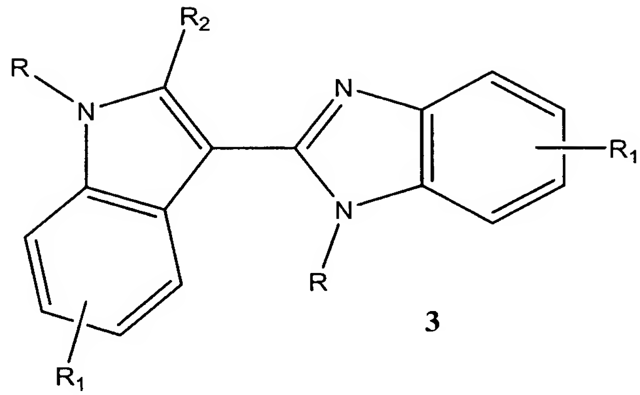
25. The compound of claim 21, wherein X represents NR; and $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl.

26. The compound of claim 21, wherein X represents NR; and $R_2$ is H, Me, or lower alkyl.

27. The compound of claim 21, wherein $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl; and $R_2$ is H, Me, or lower alkyl.

28. The compound of claim 21, wherein X represents NR; $R_1$ independently for each occurrence is absent or selected from the group consisting of halogen, amido and alkoxycarbonyl; and $R_2$ is H, Me, or lower alkyl.

29. A compound represented by generalized structure **3**:




**3**

wherein

R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, hydroxyl, alkoxyl, -$(CH_2)_n$Oalkyl, -$(CH_2)_n$Oaryl, formyl, acyl, -C(O)Oalkyl, -OC(O)Oaryl, -C(O)NHalkyl, -OC(O)NHaryl, alkylsulfonyl, -$(CH_2)_nC(O)N(R_{80})_2$, -$(CH_2)_n$-CH(OH)-$CH_2N(R_{80})_2$, or -$(CH_2)_n$-$R_{80}$;

$R_1$ independently for each occurrence is absent or present between one and four times on each fused benzo ring;

$R_1$, when present, is selected independently for each occurrence from the set consisting of Me, lower alkyl, alkenyl, -C≡C-$R_{80}$, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, halogen, hydroxyl, alkoxyl, nitro, nitroso, cyano, acyl, acylamino, amido, alkoxycarbonyl, sulfonyl, sulfonamido, acyloxy, -$(CH_2)_nC(O)N(R_{80})_2$, -$(CH_2)_n$-CH(OH)-$CH_2N(R_{80})_2$, and -$(CH_2)_n$-$R_{80}$;

$R_2$ represents H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocycloalkyl, hydroxyl, alkoxyl, -$(CH_2)_n$Oalkyl, -$(CH_2)_n$Oaryl, formyl, acyl, -C(O)Oalkyl, -OC(O)Oaryl, -C(O)NHalkyl, -OC(O)NHaryl, sulfonyl, -$(CH_2)_nC(O)N(R_{80})_2$, -$(CH_2)_n$-CH(OH)-$CH_2N(R_{80})_2$, or -$(CH_2)_n$-$R_{80}$;

$R_{80}$ represents independently for each occurrence H or an optionally substituted alkyl, acyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl moiety; and

n independently for each occurrence is an integer in the range 0 to 8 inclusive.

30. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl.

31. The compound of claim 29, wherein $R_1$ is present at least once on the B-ring of the indolyl moiety.

32. The compound of claim 29, wherein $R_1$ is present at least once on the B-ring of the

indolyl moiety; and said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety.

33. The compound of claim 29, wherein $R_1$ is present exactly once on the B-ring of the indolyl moiety.

34. The compound of claim 29, wherein $R_1$ is present exactly once on the B-ring of the indolyl moiety; and said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety.

35. The compound of claim 29, wherein $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety.

36. The compound of claim 29, wherein $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety.

37. The compound of claim 29, wherein $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety.

38. The compound of claim 29, wherein $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both.

39. The compound of claim 29, wherein $R_2$ is H, Me, or lower alkyl.

40. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; and $R_1$ is present at least once on the B-ring of the indolyl moiety.

41. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; and said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety.

42. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; and $R_1$ is present exactly once on the B-ring of the indolyl moiety.

43. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; and said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety.

44. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; and $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety.

45. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety.

46. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; and $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety.

47. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both.

48. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; and $R_2$ is H, Me, or lower alkyl.

49. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; and $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety.

50. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety.

51. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; and $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety.

52. The compound of claim 29, wherein R represents independently for each occurrence

H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both.

53. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; and $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety.

54. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety.

55. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; and $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety.

56. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both.

57. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; and $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety.

58. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl

moiety.

59. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; and $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety.

60. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both.

61. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; and $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety.

62. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety.

63. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; and $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety.

64. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both.

65. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl,

cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; and $R_2$ is H, Me, or lower alkyl.

66. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; and $R_2$ is H, Me, or lower alkyl.

67. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; and $R_2$ is H, Me, or lower alkyl.

68. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; and $R_2$ is H, Me, or lower alkyl.

69. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

70. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

71. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

72. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both; and $R_2$ is H, Me, or lower alkyl.

73. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl,

cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

74. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

75. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

76. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both; and $R_2$ is H, Me, or lower alkyl.

77. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

78. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

79. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$

is present once or twice on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

80. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present at least once on the B-ring of the indolyl moiety; said first instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both; and $R_2$ is H, Me, or lower alkyl.

81. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

82. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

83. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

84. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both; and $R_2$ is H, Me, or lower alkyl.

85. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

86. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present at least once on the B-ring of the benzimidazolyl moiety; said first instance of $R_1$ is a halogen at the 5- or 6-position of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

87. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; and $R_2$ is H, Me, or lower alkyl.

88. The compound of claim 29, wherein R represents independently for each occurrence H, Me, lower alkyl, lower heteroalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, or heterocycloalkyl; $R_1$ is present exactly once on the B-ring of the indolyl moiety; said instance of $R_1$ is a halogen at the 5-position of the indolyl moiety; $R_1$ is present once or twice on the B-ring of the benzimidazolyl moiety; said instance or instances of $R_1$ represent halogen at the 5- or 6-position of the benzimidazolyl moiety or both; and $R_2$ is H, Me, or lower alkyl.

89. The compound of any of claims 1-88, wherein said compound has an MIC less than 25 μg/mL against a Gram-positive bacterium.

90. The compound of any of claims 1-88, wherein said compound has an MIC less than 10 μg/mL against a Gram-positive bacterium.

91. The compound of any of claims 1-88, wherein said compound has an MIC less than 1 μg/mL against a Gram-positive bacterium.

92. The compound of any of claims 1-88, wherein said compound has an MIC less than 25 μg/mL against methicillin-resistant *Staphylococcus aureus*, ciprofloxacin-resistant *Staphylococcus aureus*, vancomycin-resistant *Staphylococcus aureus*, or vancomycin-resistant *Enterococcus faecalis*.

93. The compound of any of claims 1-88, wherein said compound has an MIC less than 10 μg/mL against methicillin-resistant *Staphylococcus aureus*, ciprofloxacin-resistant *Staphylococcus aureus*, vancomycin-resistant *Staphylococcus aureus*, or vancomycin-resistant *Enterococcus faecalis*.

94. The compound of any of claims 1-88, wherein said compound has an MIC less than 1 μg/mL against methicillin-resistant *Staphylococcus aureus*, ciprofloxacin-resistant

*Staphylococcus aureus*, vancomycin-resistant *Staphylococcus aureus*, or vancomycin-resistant *Enterococcus faecalis*.

95. The compound of any of claims 1-88, wherein said compound has an MIC less than 25 μg/mL against a Gram-negative bacterium.

96. The compound of any of claims 1-88, wherein said compound has an MIC less than 10 μg/mL against a Gram-negative bacterium.

97. The compound of any of claims 1-88, wherein said compound has an MIC less than 1 μg/mL against a Gram-negative bacterium.

98. A pharmaceutical preparation, comprising a compound of any of claims 1-97; and a pharmaceutically acceptable excipient.

99. A disinfectant preparation, comprising a compound of any of claims 1-97.

100. A method of treating a mammal suffering from a bacterial infection, comprising the step of: administering to a mammal suffering from a bacterial infection a compound of any of claims 1-97 or pharmaceutical preparation of claim 98.

101. The method of claim 100, further comprising the step of: repeating said administration of said compound of any of claims 1-97 or said pharmaceutical preparation of claim 98 until said bacterial infection can no longer be detected in said mammal.

**Figure 1**

Certain Aryl-Benzimidazoles of the Present Invention that were Synthesized Using a Procedure Outlined in Example 1

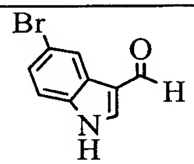
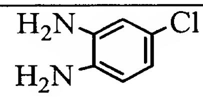
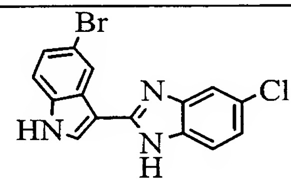
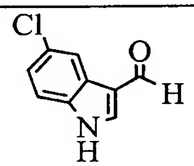
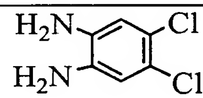
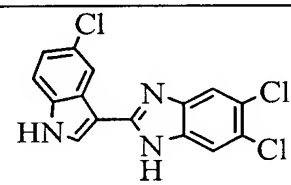
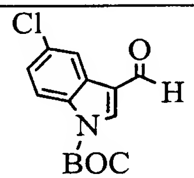
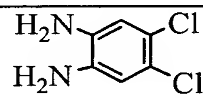
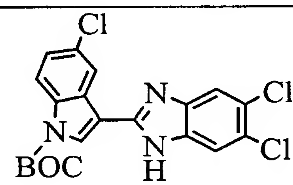
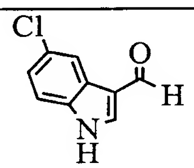
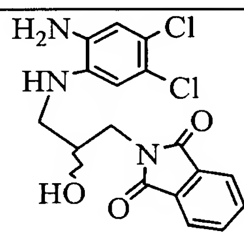
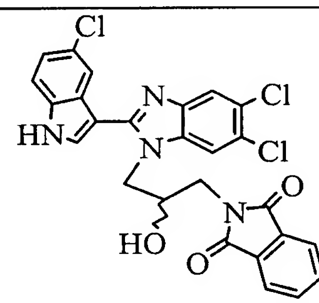
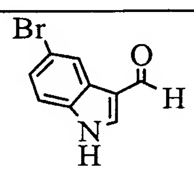
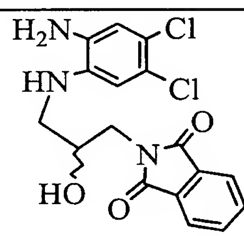
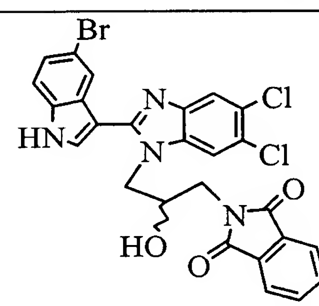
| **Arylcarboxaldehyde** | **Phenylenediamine** | **Aryl-Benzimidazole** |
|---|---|---|
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |
|  |  |  |

**Figure 2**

Certain Aryl-Benzimidazoles of the Present Invention that were Synthesized Using a Procedure Outlined in Example 1

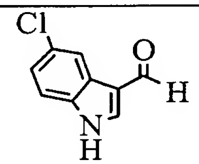
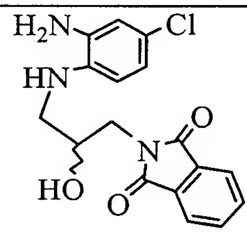
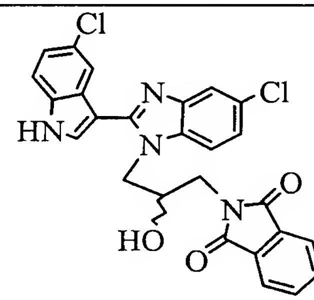
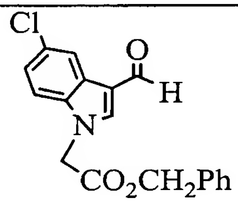
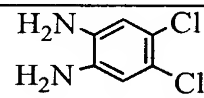
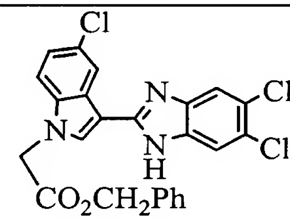
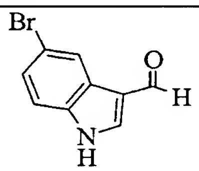
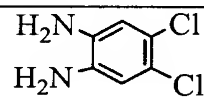
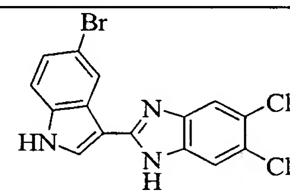
| Arylcarboxaldehyde | Phenylenediamine | Aryl-Benzimidazole |
|---|---|---|
|  |  |  |
|  |  |  |
|  |  |  |

**Figure 3**

Certain Aryl-Benzimidazoles of the Present Invention that were Synthesized Using a Procedure Outlined in Example 1

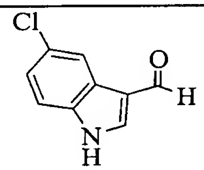
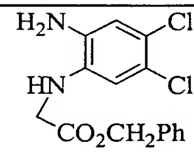
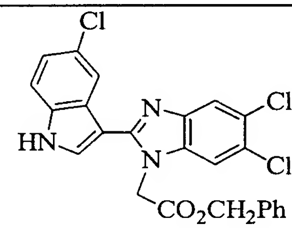
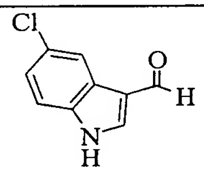
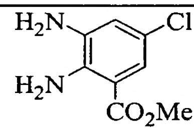
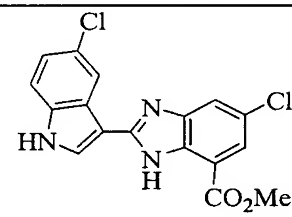
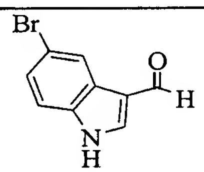
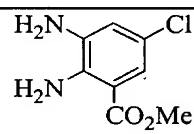
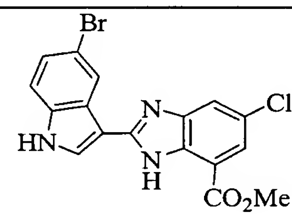
| Arylcarboxaldehyde | Phenylenediamine | Aryl-Benzimidazole |
|---|---|---|
|  |  |  |
|  |  |  |
|  |  |  |

**Figure 4**

Certain Aryl-Benzimidazoles of the Present Invention Prepared By Hydrazinolysis of Aryl-Benzimidazoles Depicted in Figures 1 and 2

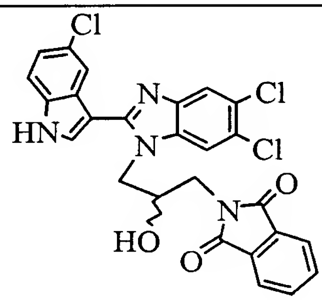
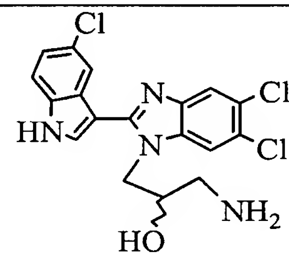
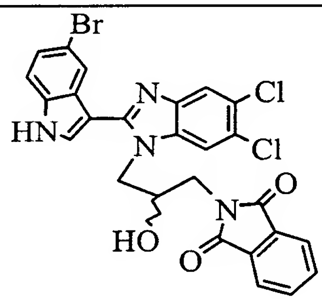
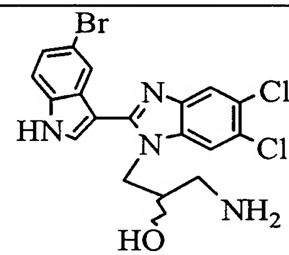
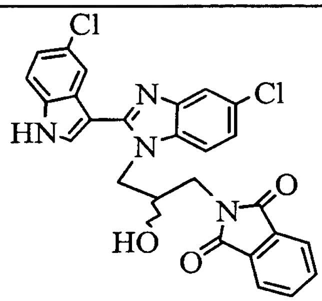
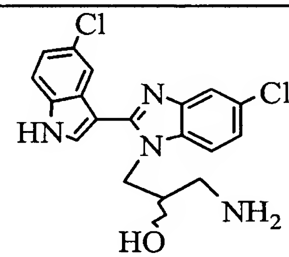
| **Starting Aryl-Benzimidazole** | **Product Aryl-Benzimidazole** |
| --- | --- |
|  |  |
|  |  |
|  |  |

**Figure 5**

Certain Aryl-Benzimidazoles of the Present Invention Prepared from an Aryl-Benzimidazole Depicted in Figure 2 By Saponification Followed by Amide Formation

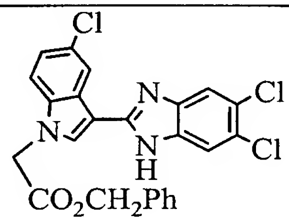
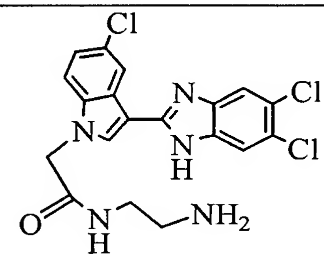
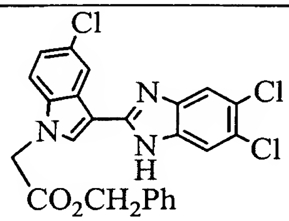
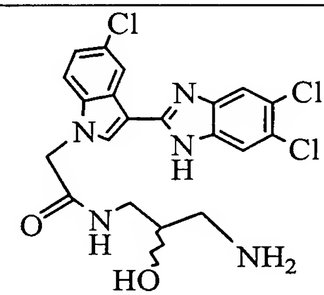
| **Starting Aryl-Benzimidazole** | **Product Aryl-Benzimidazole** |
|---|---|
|  |  |
|  |  |

**Figure 6**

Certain Aryl-Benzimidazoles of the Present Invention Prepared from an Aryl-Benzimidazole Depicted in Figure 3 By Saponification Followed by Amide Formation

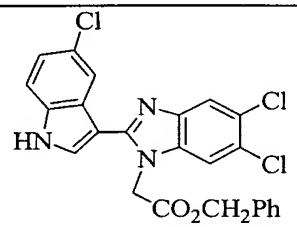
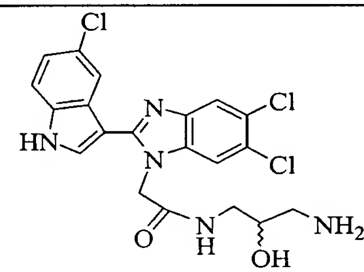
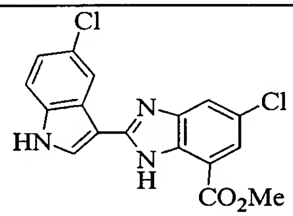
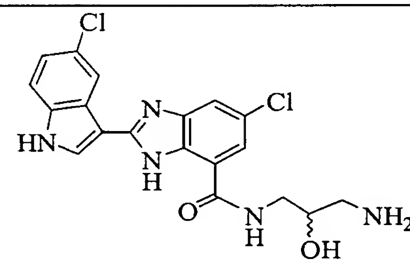
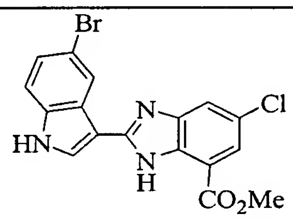
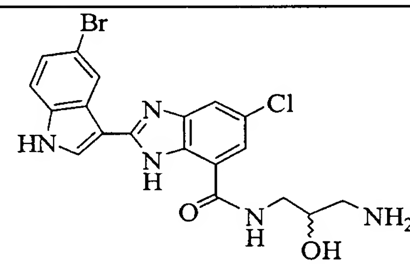
| **Starting Aryl-Benzimidazole** | **Product Aryl-Benzimidazole** |
|---|---|
|  |  |
|  |  |
|  |  |

**Figure 7**

MIC Values Against MRSA for Certain Aryl-Benzimidazoles of the Present Invention

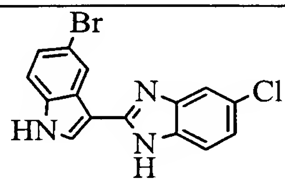
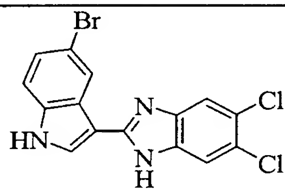
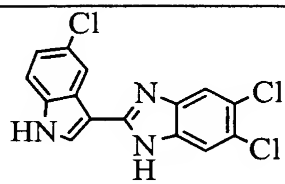
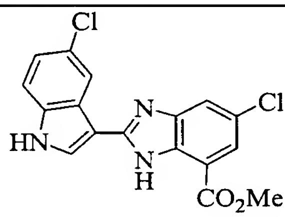
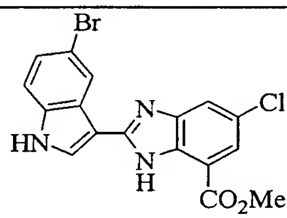
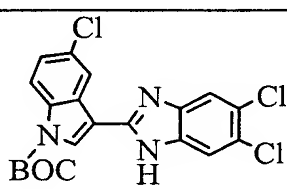
| Aryl-Benzimidazole | MIC Value Against MRSA (μg/mL) |
|---|---|
|  | <10 |
|  | <1 |
|  | <1 |
|  | >25 |
|  | >25 |
|  | <10 |

**Figure 8**

MIC Values Against MRSA for Certain Aryl-Benzimidazoles of the Present Invention

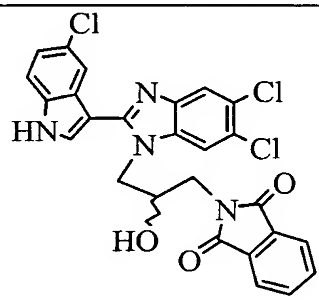
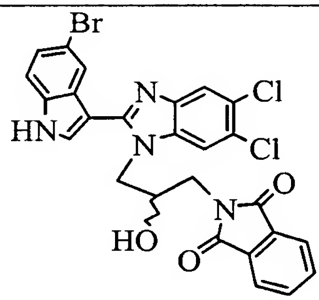
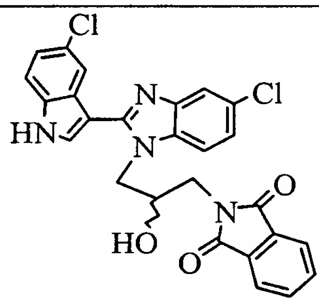
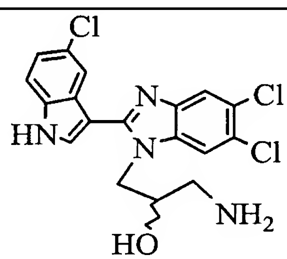
| Aryl-Benzimidazole | MIC Value Against MRSA (μg/mL) |
|---|---|
|  | >25 |
|  | >25 |
|  | >25 |
|  | <25 |

**Figure 9**

MIC Values Against MRSA for Certain Aryl-Benzimidazoles of the Present Invention

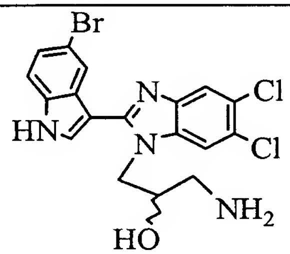
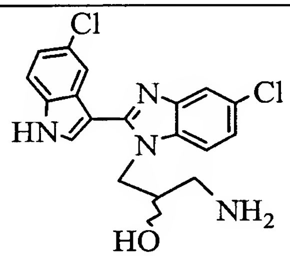
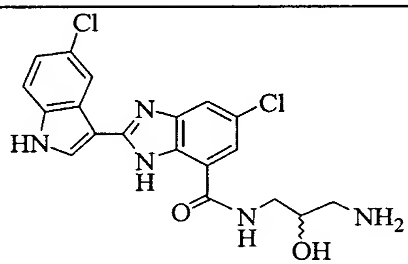
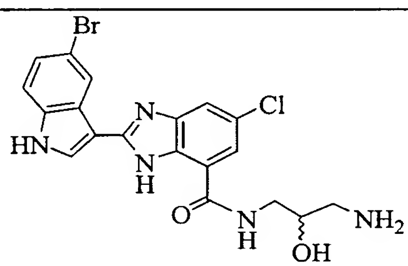
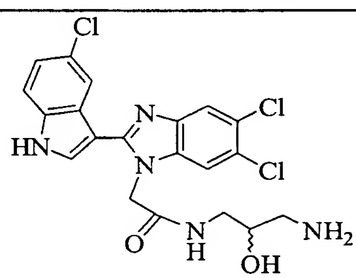
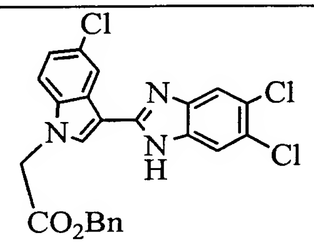
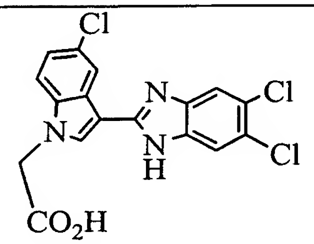
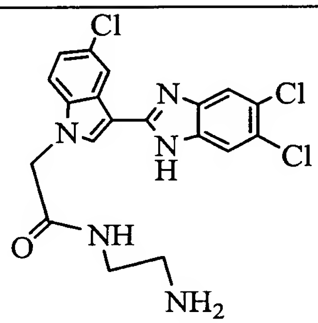
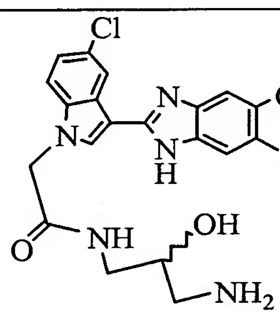
| Aryl-Benzimidazole | MIC Value Against MRSA (μg/mL) |
|---|---|
|  | <10 |
|  | >25 |
|  | <10 |
|  | <10 |
|  | <25 |

**Figure 10**

MIC Values Against MRSA for Certain Aryl-Benzimidazoles of the Present Invention

| Aryl-Benzimidazole | MIC Value Against MRSA (μg/mL) |
|---|---|
|  | >25 |
|  | >25 |
|  | <10 |
|  | <10 |

# INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/US 00/17371

**A. CLASSIFICATION OF SUBJECT MATTER**
IPC 7 C07D487/04 A61K31/404 A61K31/04 A61P31/04
//(C07D487/04,235:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, PAJ, EPO-Internal, BEILSTEIN Data, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; NGUYEN, MINH THAO ET AL: "Synthesis of indolylbenzoxazoles and indolylbenzimidazoles" retrieved from STN Database accession no. 126:225251 XP002150146 abstract & TAP CHI HOA HOC (1996), 34(3), 48-51 , --- | 1-101 |

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 16 October 2000 | 03.11.00 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Härtinger, S |

1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | DATABASE CHEMABS 'Online!<br>CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;<br>PALMER, P. J. ET AL: "Benzothiazolines as antituberculous agents"<br>retrieved from STN<br>Database accession no. 74:99932<br>XP002150147<br>abstract<br>& J. MED. CHEM. (1971), 14(3), 248-51 ,<br>--- | 1-101 |
| X | EP 0 791 582 A (OTSUKA KAGAKU KABUSHIKI KAISHA, JAPAN;ENDO, YASUHIRO; MANABE, KAN; END) 27 August 1997 (1997-08-27)<br>title of patent application<br>example 73<br>--- | 1-101 |
| X | DATABASE CHEMABS 'Online!<br>CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;<br>HUDKINS, ROBERT L.: "Synthesis of 1H-indolyl-2-benzimidazoles and 1H-indolyl-2-benzothiazoles"<br>retrieved from STN<br>Database accession no. 123:143814<br>XP002150148<br>abstract<br>& HETEROCYCLES (1995), 41(5), 1045-9 ,<br>--- | 1-101 |
| X | PATENT ABSTRACTS OF JAPAN<br>vol. 015, no. 474 (C-0890),<br>3 December 1991 (1991-12-03)<br>& JP 03 206042 A (TAKEDA CHEM IND LTD),<br>9 September 1991 (1991-09-09)<br>abstract<br>CA Reg.No. 128069-85-2<br>formula I<br>--- | 1-101 |
| X | EP 0 438 819 A (ENICHEM SYNTHESIS S.P.A., ITALY) 31 July 1991 (1991-07-31)<br>compounds F6, F14<br>example 3<br>--- | 1-101 |
| X | PATENT ABSTRACTS OF JAPAN<br>vol. 014, no. 513 (C-0777),<br>9 November 1990 (1990-11-09)<br>& JP 02 212486 A (KIRIN BREWERY CO LTD),<br>23 August 1990 (1990-08-23)<br>abstract<br>CA Reg.No. 131278-79-0<br>formulae I, II, IV<br>---<br>-/-- | 1-101 |

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EP 0 351 856 A (TAKEDA CHEMICAL INDUSTRIES, LTD., JAPAN) 24 January 1990 (1990-01-24) example 136 | 1-101 |
| X | PATENT ABSTRACTS OF JAPAN vol. 013, no. 523 (C-657), 21 November 1989 (1989-11-21) & JP 01 211580 A (TAISHO PHARMACEUT CO LTD), 24 August 1989 (1989-08-24) abstract CA Reg.No. 125537-56-6 formulae I, VII | 1-101 |
| X | DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SAKAKIBARA, JINSAKU ET AL: "Studies on the chemical transformations of rotenoids. III. Ring conversions of methyl rotenononate and.beta.-rotenonone" retrieved from STN Database accession no. 109:128693 XP002150149 abstract & HETEROCYCLES (1988), 27(2), 423-35 , | 1-101 |
| X | DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HAWKINS, DAVID G. ET AL: "Competitive cyclization of singlet and triplet nitrenes. Part 7. Reaction paths of 2-azidophenyl benzothienyl sulfides" retrieved from STN Database accession no. 92:128157 XP002150150 abstract & J. CHEM. SOC., PERKIN TRANS. 1 (1979), (12), 3207-10 , | 1-101 |

1

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/17371

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 100 and 101 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [X] Claims Nos.: 1-64
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box I.2

Claims Nos.: 1-64

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible.

Moreover, the present claims 1-88 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables and possible permutations that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Even when taking into accountg the definitions provided for the vague and "open" groups, such as "aryl, heteroaryl, heterocyclyl, or polycyclyl" no meaningful search is possible, basically due to the fact that these moietes embrace arbitraily substituted alternatives, which semselves may be substituted and/or part of further ring systems (cf. description pages 9, 10, 16). Furthermore, support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed, i.e. only for indol-3-yl-benzimidazole derivatives. Consequently, the search has been carried out for those parts of the application which do appear to be clear, concise, and which represent a reasonable generalization over the individualized compounds of the invention, namely the group of compounds claimed in claims 65 to 88, all of which fall under the general formula 3.

As to the subject-matter of claims 89-97, a meaningful search of quantitative activity data was not possible. The search was restricted to the underlying compounds insofar as they relate to products of claims 65-88.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]tional Application No
PCT/US 00/17371

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 0791582 A | 27-08-1997 | JP 9048755 A | 18-02-1997 |
| | | JP 2935102 B | 16-08-1999 |
| | | JP 10017548 A | 20-01-1998 |
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